REMARKS

The Applicants will now address the Examiners' rejections in the order presented in the office action.

Claim Rejections-35 USC §112, 1st paragraph

Claims 1, 8, 15, 16 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Regarding claims 1, 8, and 15, the Examiner will note that Applicants have amended these claims to recite "E2F binding sites" in lieu of an "E2F responsive transcriptional nucleotide regulatory site." Clearly, this is an enabled aspect of Applicants' invention, and important in that it is the realization that such sites are part of the E2F promoter element that affects viral replication or gene expression in the context claimed by the Applicants. Thus, this amendment should obviate the rejection.

Regarding claim 16, the Examiner has rejected this claim stating that Applicants' Specification is enabled only for claims limited to "a method for killing cancer cells, comprising the steps of directly injecting to a cell population comprising cancer cells and normal cells the adenoviral vector of 1), thereby killing said cancer cells in the presence of the normal cells." The Examiner has cited several references that stand for the proposition that, in the Examiner's view "it is not apparent how any of the E2F responsive promoter, let alone other unspecified E2F responsive regulatory sites, is distributed and/or targeted only in a desired *in vivo* cancer cells for replication and subsequent expression of a heterologous gene, thereby generating any therapeutically useful effect..." The Examiner further states that Applicants' invention claims are not enabled for a) administration other than by direct injection, and (b) the expression of heterologous genes. Applicants beg to differ with the Examiner for the following reasons.

First, the Examiner will note that certain of the cited references show the use of organ or tissue specific viral vectors. For example, in the case of Russell there is described the use of viral vectors that replicate selectively in liver cells via an albumin promoter, or B-cells

through the use of an immunoglobulin promoter, while Miller describes the use of viral vectors that target melanoma cancer cells through the use of a tyrosinase promoter. In this regard it is important to note that the regulator element, E2F, that Applicants describe and claim in the context of their adenoviral vectors is *cancer cell specific for a certain class of cancer cells*, that is, cancer cells that have the pRB-pathway disrupted. This, in part, distinguishes Applicants' vectors from those of both Russell and Miller. Thus, it is respectfully not seen how the work of Russell or Miller is applicable to support a lack of enablement for Applicants' claims.

Second, Vile et al and Gomez-Novarro et al., Applicants submit, support their position that their claims are enabled. Vile et al., stand for the proposition that it is a *combination* of regulatory elements including enhancers/silencers/promoters that may give rise to a loss of *viral target cell specificity*. Gomez-Novarro et al., stand for the proposition that "certain tumor-specific regulatory elements lose their specificity in the context of an adenoviral vector." Consider the experimental results of Johnson et al.,Cancer Cell, vol. 1, pp 325-337, May 2002, copy enclosed. They show the use of the invention adenovirus, Onyx-411, which has the E2F promoter, to selectively kill a certain class of cancer cells. They further show that wild-type adenovirus kills such cancer cells to a similar degree as Onyx-411. Thus, the insertion of the E2F promoter in Onyx-411 does not cause a loss of adenoviral cell specificity. That is, since the wild-type virus lacks the E2F promoter, these results support that Applicants' invention is not limited by a *combination* of regulatory elements.

Finally, Yanez, and Anderson and Mastrangelo et al., stand for the proposition that the efficiency of gene targeting is low, and there are major deficiencies in gene transfer or expression, respectively, The Examiner has stated that it is "not apparent how any of the disclosed tissue-specific vectors when used in the context of an application of an E2F responsive promoter...is distributed and/or targeted only in a desired *in vivo* cancer cells for replication and subsequent expression of a heterologous gene..." Further, the Examiner has queried how such tissue-specific promoters are regulated *in vivo* from the claimed adenoviral vectors to avoid toxicity to normal cells *in vivo*. First, Applicants note that their adenoviral vectors replicate selectively in a specific type of cancer cell, that is, cancer cells that have the

pRB-pathway disrupted, AND this can be achieved by systemic administration Consequently, with regard to the expression of a heterologous gene in such cancer cell, this will occur if the cancer cell has the pRB- pathway dispruted. Second, and importantly, with regard to toxicity, another aspect of Applicants' invention adenoviruses is that they show reduced replication in normal cells compared to cancer cells, the reason being that normal cells do not have the pRB-pathway disrupted. Hence, Applicants' invention viruses would show reduced toxicity in normal cells with or without a heterologous gene.

The Examiner's attention is again respectfully directed to the paper by certain of the inventors of the instant patent application; that is, Johnson et al., Cancer Cell, vol. 1, pp 325-337, May 2002. There the authors test the anticancer effects of one the invention viruses, Onyx-411. In the section of the paper under the header "In vitro and in vivo efficacy of pRB-regulated adenoviruses," they state:

> "We next evaluated the systemic antitumor efficacy of ONYX-411 in nude mice (n = 10/cohort) bearing subcutaneous (s.c.) C33-A human xenograft tumors. A total dose of 2 × 109 pfu *was administered intravenously* as a daily regimen of 4 × 108 pfu for five consecutive days. Both ONYX-411 and wild-type virus (dl309) demonstrated a significant survival advantage relative to vehicle control (p = 0.03 and 0.005, respectively), and resulted in equivalent numbers of complete regressions (CRs: N = 3/10; Figure 8A). Similar levels of ONYX-411 and dl309 virus replication were observed in tumor samples by in situ hybridization at 60 and 66 days post treatment, respectively (Figure 8B). In two independent studies using the C33-A cervical cancer xenograft model, increasing the dose of ONYX-411 by approximately 2-fold (3.75 × 109 pfu total, administered as 7.5 × 108 pfu on days 1–5) resulted in a comparable survival advantage at day 70 (range: 60%–70% of mice) ***without increased toxicity (Figure 8A).*** In these studies, cure rates ranged from 25%–60% (Figure 8A). Subsequent studies have also demonstrated that ONYX-411 can be administered systemically in tumor bearing, immunocompromised mice (Balb/c genetic background) at doses up to a total of 5 × 109 pfu (1 × 109 pfu administered on days 1–5) with no increased toxicity. " (Emphasis added).

Note that in the above excerpt, *the method of administering Onyx 411 is by intravenous injection, and importantly, as also stated in the cite, intravenous admininistration is efficacious.* The Examiner stated in the Office Action that Applicants have given no evidentiary support for their position that their claims are enabled for *in vivo* therapeutic applications. The Applicants respectfully submit that the above cited Johnson et al., paper

provides the requested evidentiary support. Thus, Applicants respectfully request that the rejection be withdrawn.

The Examiner has cited Meng et al., which, in part, teach that because xenograft models, more specifically nude mice, lack a fully functional immune system, it is possible that administering the invention virus, other than by direct injection into the tumor, would fail in humans that do have a fully functional immune system. As the Examiner knows, a patent need not teach, and preferably omits what is well known in the art. Hybritech, Inc., v. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1384, 231 USPQ 81, 94. Thus, Applicants disagree for the following reasons, which are well known in the art.

First, those individual that have never been exposed to adenovirus do not have circulating antibody to the virus, AND would not develop such antibody for at least a week or more, which is typically the time it takes to develop an antibody response to most antigens. Thus, during this time a patient can undergo several treatments with the invention virus before an immune response would be elicited.

Second, there are at least two companies, Onyx pharmaceuticals and Sunway Pharmaceuticals, that have independently conducted clinical trials with recombinant adenovirus and reported significant anti-tumor response even in the presence of circulating antibody to adenovirus.

Third, for those patients that have high titers of adenovirus antibody prior to receiving treatment with the invention viruses, or that develop antibody during treatment, could be treated in several art recognized ways to suppressive antibody production. Immunosuppressive drugs are routinely and widely used to suppress the immune system, and have been for decades. Additionally, there are several devices that a skilled practitioner of this art would know to use to remove antibody from a patient prior to, or during treatment.

Thus, based on the Johnson et al paper, and the reasons discussed above, Applicants believe that their claims are fully enabled for administration of the invention viruses by means other than direct injection into a tumor.

Claim Rejections-35 USC §112, 2nd paragraph

Claim 7, 8, 11-12, 14-16 are rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Regarding Claim 7, the Examiner has stated that this claim is indefinite in the recitation of "substantially" because it is not apparent what is considered to be within the metes and bounds of "substantially facilitate viral replication." The Examiner will note that Applicants have deleted "substantially" from the claim.

The Examiner has also noted that Claim 7 recites "viral replication" and the Examiner has requested clarification. The Examiner will note that Applicants have amended Claim 7 to recite "adenoviral replication."

Finally with regard to Claim 7, the Examiner has suggested that inserting "binding site" after "Sp1, ATF, NF1 and NFIII/Oct-1 would clarify what Applicants intend by this recitation. Applicants have amended the claim as suggested by the Examiner.

The Examiner has remarked that Claim 8 and its dependent claims, lack antecedent basis in the recitation of "said viral gene." The Applicants have amended Claim 8 to claim "said early adenoviral gene."

Finally, regarding Claim 15, the Examiner has stated that the phrase "said transcriptional regulatory sequence" is not clear. The Examiner will note that Applicants have amended Claim 15 to clarify that what is intended in a human E2F-1 *promoter*.

The Examiner will note that Applicants have added a new claim, claim 17.

Applicants have addressed all the rejections presented by the Examiner, and earnestly believe that their application is in condition for allowance. However, should the Examiner has any questions with regard to this amendment, the Examiner is encouraged to call the undersigned at: 510-596-6502.

Extension of Time Pursuant to 37 C.F.R. § 1.136(a)

A Petition for 3 Month extension of time is being filed concurrently with this response. Applicant respectfully requests a 3 -month extension of time to file a Response to the Non-Final Office Action mailed September 9, 2004. The extended period expires on March 9, 2005.

The Commissioner is authorized to charge any fees associated with this communication to Deposit Account No. 15-0615 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: 3/9/05

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